REMARKS

Applicants submit this response to the Office Action dated October 21, 2003. Accompanying this response is a Petition to Revive for Unintentional Abandonment, due to nonreceipt by Applicant of the original Office Action.

In the Office Action, the Examiner noted that the specification should be amended to correct the reference to Figures 2A-2B, 3A-3B, etc. This has been addressed by amendment herein. Applicants have also submitted corrected drawings. Withdrawal of this objection is respectfully requested.

Claim 16 is objected to for being of improper dependent form, and this has been addressed by amendment herein, as has the objection to claim 18 in view of a typographical error.

Claims 15-18 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly is directed to non-statutory matter. The Examiner suggested amending the claims to recite "an isolated polypeptide, comprising at least 14 contiguous amino acids . . . ." Claim 14 has been amended accordingly. The Examiner also stated that the recitation of "epitope bearing portion" was not necessary in view of the recognition in the art that a protein of 5-6 amino acids is sufficient to generate an antibody. Claim 15 has been amended accordingly.

Claims 15-18 allegedly fail to include limitations that would distinguish the claimed proteins from those found in nature. The Examiner suggested amending the claims to recite a purity limitation.

Applicants have amended claims 14 and 15 as suggested by the Examiner, as supported in the specification at, for example, at page 13, lines 6-9. However, for completeness of the record, applicants have addressed the case law cited by the Examiner. *Diamond v. Chakrabarty,* 206 USPQ 193 (1980), did establish the "hand of man" as being relevant in the patentability of genetically engineered microorganisms. *Ex parte Siddiqui,* 156 USPQ 246 (1966), was cited in support for the statement that purity of a naturally occurring product does not necessarily impart patentability. *Siddiqui* relates to a compound obtained by a series of "extractions and neutralizations." In contrast, applicants did not obtain FGF-23 simply by extracting it from a natural source. Instead, as described in the specification, it is a product of a laboratory construct not found in nature, namely, DNA obtained by amplification of cDNA, cloned into a vector, and expressed as a recombinant protein in insect cells. The Examiner has offered no evidence that

FGF-23 is obtainable through a method analogous to that described in *Ex Parte Siddiqui*. However, *Merck Co. v. Chase Chemical Co.*, 273 F. Supp. 68 (1967), was cited to support the statement that when purity results in a new utility, patentability is considered. By analogy, applicants have provided isolated FGF-23 that is novel. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 12-18, 22 and 61-65 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly has no specific and substantial credible utility. Responding to the arguments and Declaration filed on June 3, 2003, the Examiner states that the specification does not disclose use of the claimed invention for lowering serum phosphate levels, nor which diseases the claimed invention could be used for treating. Applicants request reconsideration and withdrawal of the rejection.

At page 7, lines 28-29, the specification specifically cites, and incorporates by reference, *Nature Genetics* 26:354-358 (2000), which discusses disorders of phosphate metabolism. According to Dr. Kavanaugh's Declaration, of record, administration of a non-cleavable FGF-23, as supported in the specification, lowered serum phosphate levels in mice. This finding is consistent with studies described in the *Nature Genetics* publication. The publication describes families afflicted with the disease known as autosomal dominant hypophosphataemic rickets, in which patients exhibit low serum phosphorous concentration, among other symptoms. The authors describe a mutation analysis designed to identify linkages between carriers of the disease, and mutations in specific genes. They found missense mutations in a member of the fibroblast growth factor family of proteins, which they identify as FGF23. The authors further report this to be the first mutation identified in the FGF family (page 347, last full paragraph). However, they did not identify the mechanism of action.

Thus, it is of record in the application, by virtue of the *Nature Genetics* article incorporated by reference, that a mutation in FGF-23 is associated with a disease state that manifests as lower serum phosphate. The present applicants have identified a mechanism by which this occurs, by replicating the decreased serum phosphate level phenotype in mice administered with FGF-23 engineered to contain an amino acid change that prevented cleavage of the FGF-23. This is discussed in detail in the Declaration of Dr. Kavanaugh, of record and as filed on June 3, 2003.

In the present Office Action, the Examiner states at page 6, paragraph 11, that the asserted utility was not substantial, because further research allegedly was needed to confirm a utility. The Examiner also stated that no specific benefit exists in currently available form.

Applicants respectfully disagree. A disease, autosomal dominant hypophosphataemic rickets, discussed above, is linked to mutations in FGF-23 at precisely the location that applicants have identified as a physiologically important cleavage point. Subsequent publications have further confirmed that FGF-23 plays a substantial role in regulating phosphate levels in the human and other mammals. See, for example, Ward, L.G., *et al., Bone* 34:905-911 (2004) (hypophosphatemic rickets resolved following removal of an FGF-23 producing tumor); Shimada, T. *et al., J. Bone Mineral Res.* 19:429-435 (2004) (FGF-23 is a regulator of phosphate metabolism *in vivo*, and FGF-23 injection reduced serum phosphate levels); Blumsohn, A., Curr. *Opin. Nephrol. Hypertens.* 13:397-401 (2004) (FGF-23 knock-out mouse shows hyperphosphatemia); and Shimada, T. *et al., Endocrinology* 143:3179-3182 (2002) (confirming the present applicants' results showing that mutant FGF-23 was not cleaved between positions 179 and 180, and that mutant FGF-23 expressed by cells implanted in mice caused hypophosphatemia and decrease in bone mineral content). These publications are filed herewith as Exhibits 1-4.

Finally, although clinical trials are not required in order to confirm the utility of an invention, applicants note that a clinical trial by the NIH (NIDCR) is underway to study the role of FGF-23 in phosphorous regulation (Exhibit 5). Such clinical trials would not take place absent *in vitro* and animal studies providing abundant evidence of a role for FGF-23 in this precise pathway.

For the foregoing reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 101 are respectfully requested.

Claims 12-13 and 61-65 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in view of the language "wherein said polypeptide retains the biological activity of human FGF-23." In support, the Examiner cited several cases, two of which date from 1948-49. *Ex parte Wu,* 100 USPQ 2d 2031, 2033 (Bd. Pat. App. & Inter., 1989), was cited for use of the term "such as." The Examiner stated that the following aspect of this case is relevant here: is the language merely exemplary and not required, or is it a required feature of the claims? The *Wu* decision actually construes the term "optionally," not the term

"such as," which was interpreted in a prior case that the *Wu* Board distinguished in reaching a decision that Wu's claims were in fact not indefinite under 35 U.S.C. § 112, second paragraph. Furthermore, the Board in *Wu* stated that the determination of compliance with §112, second paragraph, "necessarily depends on the facts of each particular case or application," (100 USPQ 2d at 2033). Since claims 12-13 and 61-65 as amended herein contain neither "such as" or "optionally" or similar terms, *Wu* is inapplicable. The Examiner also cited three other cases, none of which support the ground of rejection. *Ex Parte Steigewald,* 131 USPQ 74 (Bd. App. 1961) does not support the Examiner's position because the present claims do not recite the term "such as," and as pointed out in reference to *Wu*, the facts of each particular case are important in interpreting a phrase for compliance with §112, second paragraph. *Ex parte Hall,* 83 USPQ 38 (Bd. App. 1948). also fails to support the position because it construes the term "such as," which is not recited in the present claims. Finally, *Ex parte Hasche,* 86 USPQ 481 (Bd. App. 1949), is not on point because it construes the terms "which may be" and "such, for example, as" which are not recited in the present claims.

Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claim 13 is rejected under 35 U.S.C. § 102(b) as being anticipated by Smallwood *et al.,* (*P.N.A.S.* 93:9850-9857, 1996). In view of the amendment to claim 13 herein, applicants submit that this ground of rejection may be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
Nobuyuki Itoh et al.
DAVIS WRIGHT TREMAINE LLP

By 
Jane E. R. Potter
Registration No. 33,332

2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688
Phone: (206) 628-7650
Facsimile: (206) 628-7699